# α-Fetoprotein

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## ABSTRACT

α-Fetoprotein (AFP) measurements have clinical implications in fetal medicine and, in infants and older children, in detection, differential diagnosis and monitoring of malignant disease. Maternal serum AFP levels constitute part of a multiple-marker test used in early second-trimester screening to predict risk of fetal chromosomal abnormalities. Those individuals with increased risk are offered further definitive diagnostic investigation. Second-trimester screening is now increasingly being superseded by first-trimester screening with other serum markers and ultrasound. As AFP is only produced physiologically during fetal development, elevated serum levels after the first two post-natal years usually indicate the presence of a malignant disease process. Before this time, levels may be purely physiological and therefore serial values should be plotted on a logarithmic chart to ensure that they are falling appropriately, with a typical half-life of ~5-6 days. If not, further investigation should be undertaken. Serum AFP is raised in a significant proportion of germ cell tumours (GCTs), hepatoblastoma and hepatocellular carcinoma (HCC). In suspected cases of GCT, serum human choriogonadotropin (HCG) estimation should also be performed. For possible intracranial GCTs, both serum and cerebrospinal fluid levels of AFP and HCG should be measured, ideally before neurosurgical biopsy. In malignant conditions, serum AFP may be used for diagnosis, treatment monitoring, surveillance for disease recurrence and prognostication. Immunohistochemistry for AFP using antibody staining is routinely used to assist pathological diagnosis on tissue sections where the differential includes GCT, hepatoblastoma and/or HCC. Elevations of serum AFP also occur in non-malignant conditions such as chronic liver disease.

## INTRODUCTION AND PHYSIOLOGY (WHAT IS α-FETOPROTEIN? WHAT IS ITS ROLE? HOW AND WHEN IS IT PRODUCED?)

α-Fetoprotein (AFP) is a glycoprotein comprising an α-globulin (~600 amino acids) with a carbohydrate moiety. It usually exists in monomeric form (ie, as a single polypeptide chain) with a molecular weight of ~70 kDa. AFP is the principal serum binding protein in the fetus, and is believed to have an important role carrying various ligands such as hormones, fatty acids, bilirubin and minerals. In the first trimester of fetal development, AFP is produced by the yolk sac,[1] a membranous sac attached to the embryo which functions as the initial circulatory system before the formal internal circulation is established. AFP production from the yolk sac diminishes rapidly after the first trimester as the sac becomes atretic.[1] From the fourth week of gestation, AFP is also produced by the fetal liver, which is the main source throughout fetal development, with the fetal gastrointestinal tract also producing trace amounts of AFP.[1] Postnatally, AFP is gradually replaced by albumin, which is exclusively derived from the liver. From an evolutionary perspective, it is notable that both AFP and albumin have significant structural homology,[2] implying shared ligand binding sites and function. Furthermore, the observation that the genes for both proteins are located within just 10 kb of each other on chromosome 4 at 4q13.3,[3] suggests a common mechanism regulating the process by which hepatocytes 'switch' from AFP to albumin production in late fetal development.

As a result of this physiological fetal AFP production, levels are usually highly elevated at birth (mean value 41 687 ng/ml or 35 017 kU/l in term infants; conversion 1 ng/ml=0.84 kU/l), with significant variation in values between individuals.[4] The half-life of AFP is usually about 5–6 days[4] and levels fall gradually to normal adult values (<10 kU/l) over time. However, it should be noted that at 2 years of age, values up to 73 kU/l are still within normal confidence intervals,[4] which reflect the wide variation in levels observed between individuals. Consequently, interpretation of isolated AFP values in the neonate and infant is meaningless and not recommended. Any relevant clinical decision making in this age group should be based on serial AFP measurements. These values should be plotted on the logarithmic scale of a formal AFP chart (see figure 1 and online supplementary figure S1) and should fall in a linear fashion. As elevated values may be due to both malignant and non-malignant disease states, further investigation is warranted if the decline in levels does not follow this linear pattern. In patients over approximately 2 years of age, when levels are <10 kU/l in most individuals, interpretation of a single AFP value is considered acceptable.

## TECHNICAL BACKGROUND (HOW IS AFP MEASURED?)

Immunoelectophoresis was originally used for AFP detection,[1] but this method was not particularly sensitive, so in the 1970s radioimmunoassays and then enzyme immunoassays were developed, followed by a variety of other detection methods in the 1980s. These techniques have now been superseded by a quantitative automated chemiluminescent sandwich enzyme immunoassay, first described in 1991[5] and refined since then. During this process, the serum sample is placed onto a magnetic bead or plate to which an anti-AFP antibody is prebound. A second detection antibody, with a chemiluminescent probe attached, is then added to the bead/plate in excess, which binds all AFP present. The AFP is thus 'sandwiched'

between two antibodies. Unbound detection antibody is then washed off. A mixture of organic substrates is then added ('developer') which makes the probe luminescent. This is detected by a chemiluminometer, and quantification in ng/ml or kU/l is performed by measuring the result against known AFP standards (see figure 2). Assay results from different manufacturers generally shown high levels of agreement as they are all standardised to WHO International Standard 72/225 (http://www.who.int/biologicals/en/). However, it should be noted that in very rare instances, assay interference may occur. For example, where very high AFP levels are being detected using a one-step assay method, AFP may occasionally simultaneously bind both capture and detection antibody (known as 'hooking'), so that the 'sandwich' cannot be formed. As a result, very high values may appear falsely low.[6] This does not occur with two-step assays, where the capture antibody step is performed first, before the detection antibody is added. However, the one-step method remains in wide use as it is a quicker to perform and more convenient than the two-step approach. If in any clinical doubt, a simple dilution study should be requested which will highlight the problem, as the AFP will suddenly appear elevated during the dilution process.

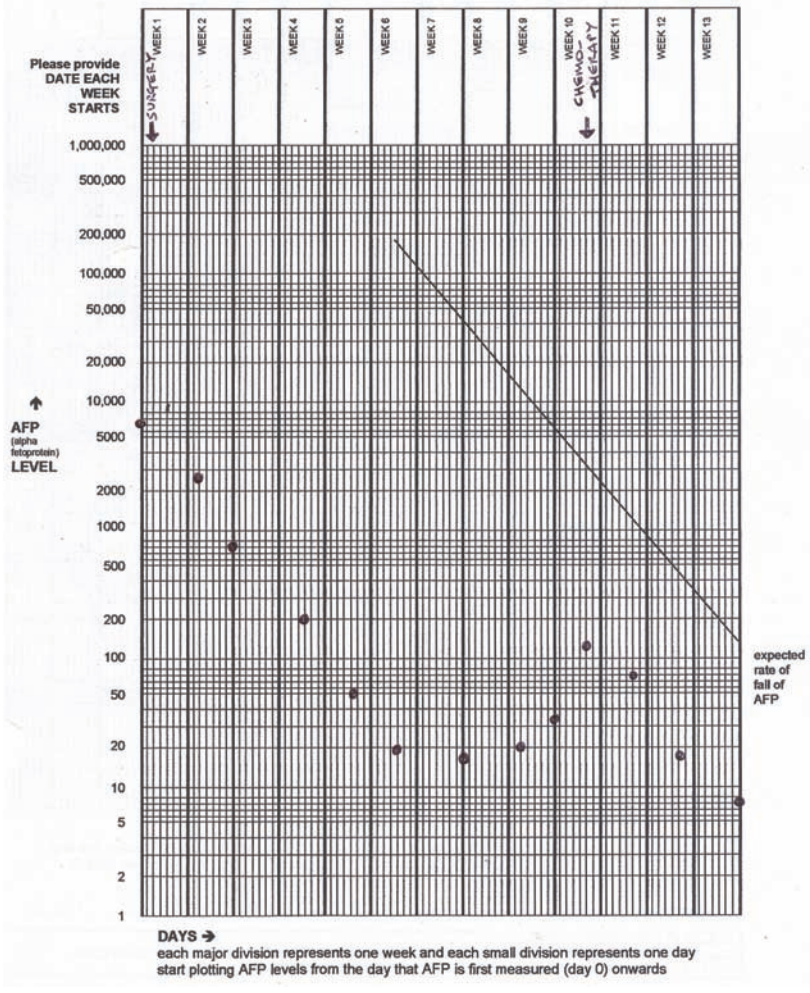


**Figure 1** A logarithmic chart used to plot serial serum AFP values. Concentration in ng/ml or kU/l is plotted on the y-axis with time on the x-axis. Levels should fall linearly at the same rate as indicated on the chart. Failure to follow this pattern indicates either increased production (eg, tumour) and/or reduced clearance (eg, Beckwith–Wiedemann syndrome) leading to an increased half-life. Depicted on the chart is an initial linear fall in AFP following definitive surgical excision of a stage I (localised) testicular malignant germ cell tumour. A subsequent increase in AFP is observed during marker surveillance caused by disease relapse, successfully treated with chemotherapy. AFP, α-fetoprotein.

## INDICATIONS (HOW IS AFP USED?)

### Malignant disease

As a tumour marker, AFP is produced by some germ cell tumours (GCTs) and the primary liver cancers hepatoblastoma and hepatocellular carcinoma (HCC) before being secreted into the bloodstream. Consequently, serum AFP measurement has been a standard investigation in the diagnostic work-up of these tumours since the 1970s. AFP has been shown to be important for diagnosis, assessment of treatment response, detection of recurrence and prognostication.

In any patient presenting with a midline mass, a GCT should be considered and levels of AFP measured along with human choriogonadotropin (HCG).[7] The use and interpretation of HCG values in patients with suspected GCTs is, however, beyond the scope of this review and discussed in more detail elsewhere.[7] Hepatoblastoma is a rare embryonal primary liver tumour affecting children predominantly under 4 years of age. The vast majority of HCC occur in patients with cirrhosis secondary to alcoholic liver disease or chronic hepatitis B and C infections, although they may rarely be caused by syndromes such as α1-antitrypsin deficiency, porphyria, glycogen storage disorders and haemochromatosis.[8] Consequently, HCC primarily affects adult patients, with only a small proportion of cases in children.

### In a child with a suspected extracranial GCT, does raised serum AFP (or HCG) confirm the diagnosis and obviate the need for surgical biopsy and histological confirmation?

AFP and HCG are valuable markers in making a diagnosis of a malignant GCT (see table 1), but the majority of extracranial cases require surgical biopsy and histological confirmation. The only exception to this rule is if the risks of surgery are deemed excessive (eg, some large mediastinal GCTs), when diagnosis may be made on the presence of elevated tumour markers and consistent radiological appearances alone.[7] Although normal serum/cerebrospinal fluid (CSF) AFP levels are <12 ng/ml (<10 kU/l), the threshold to be classified as marker-positive is higher (>25 ng/ml (>21 kU/l) in the UK). Raised AFP usually denotes the presence of the GCT subtype yolk sac tumour (YST), which may occur as either as a 'pure' malignant GCT (typically occurring early in childhood) or as a component of a 'mixed' tumour (in older children and adolescents); the latter contain teratoma or other malignant GCT elements. Moderately

elevated AFP levels may also be seen in some embryonal carcinomas and immature teratomas.

### In a child with a suspected intracranial GCT, does raised serum or CSF AFP (or HCG) confirm the diagnosis and obviate the need for neurosurgical biopsy and histological confirmation?

It was first noted that serum and/or CSF AFP levels may be elevated in intracranial GCTs in 1979.[9] Since then, measurement of serum *and* CSF levels of AFP and HCG has become standard practice in brain tumours with radiological features consistent with GCT,[7] as some secreting intracranial GCTs have elevated markers in one compartment only. Normal serum levels should lead to CSF markers being measured either at the time of emergency CSF diversion for raised intracranial pressure (RICP) or by lumbar puncture if RICP is absent. This should be undertaken prior to neurosurgical biopsy,[10] as elevations in either compartment over defined thresholds, combined with typical neuroradiological findings, are diagnostic and obviate the need for surgery and the associated potential for morbidity.[7 10] If marker-negative, patients should then proceed to diagnostic biopsy (not attempted resection). Accurate diagnosis is particularly important for intracranial GCTs as treatment for those with a secreting component is more intensive than for germinoma and the prognosis less favourable.[7]

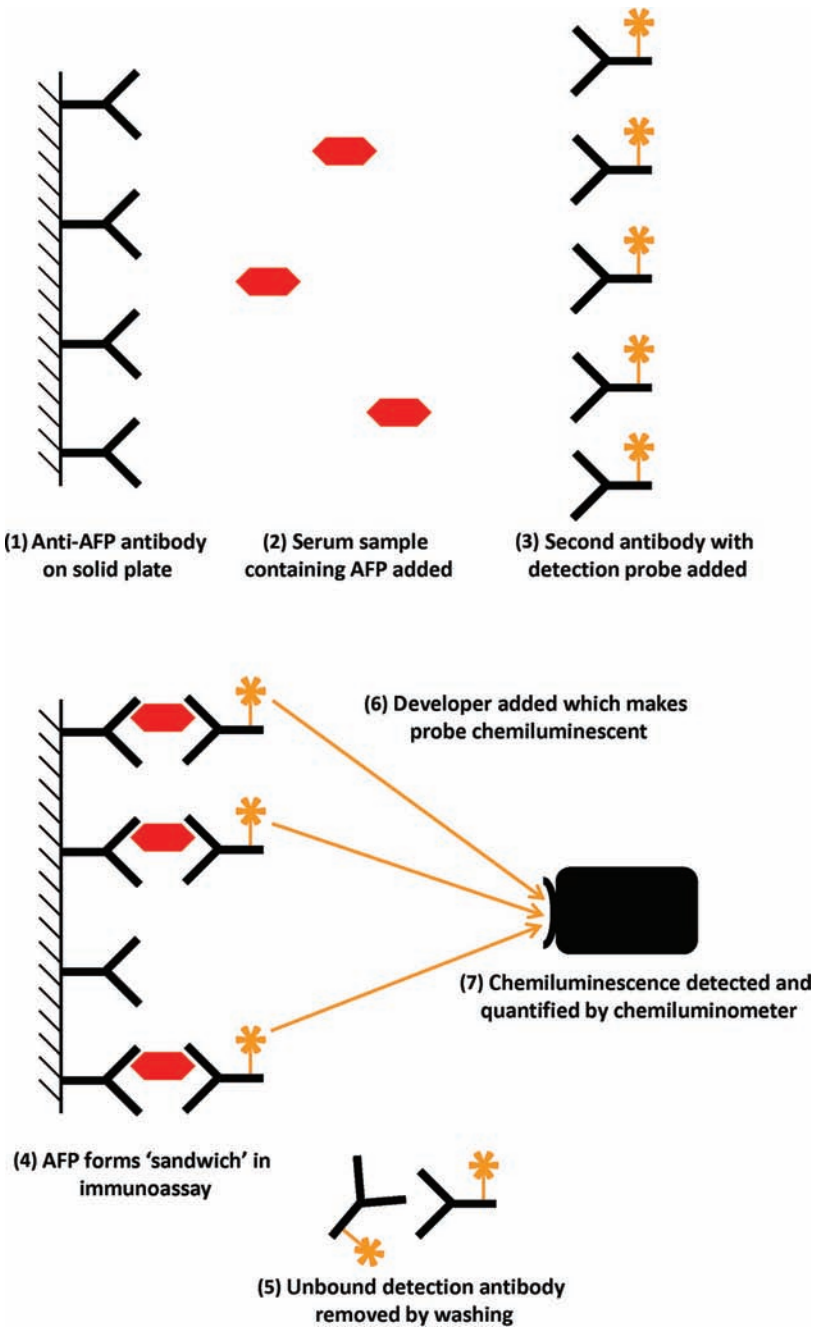


**Figure 2** Schematic of the chemiluminescent sandwich enzyme immunoassay used to detect AFP. AFP, α-fetoprotein.

### In a child with a confirmed extracranial benign immature teratoma, does raised serum AFP at diagnosis have any prognostic significance?

In immature teratomas, and consistent with production in fetal development,[1] moderately raised AFP may be due to the presence of microscopic foci ('microfoci') of YST tissue termed Heifetz lesions[11] or due to foci of immature gastrointestinal or liver tissue. The prognostic significance of Heifetz lesions in immature teratomas is controversial, with a German study suggesting that they are predictive of recurrence at any anatomical site,[12] whereas a large UK study did not detect any difference in outcomes.[11] Notwithstanding, current UK guidelines for extracranial GCTs advise that in patients presenting with immature teratomas and an initial AFP level of >1000 kU/l, treatment with chemotherapy is considered after diagnostic biopsy or resection.[11] For other teratomas (ie, all those with AFP <1000 kU/l), recommended management in the UK comprises complete surgical resection followed by close surveillance with clinical examination and serial AFP estimations in follow-up, as malignant recurrence in childhood (~2.5% of teratoma cases overall[11]) is almost invariably as a YST.[11] It should be recognised that this is a controversial area and different national oncology groups may have slightly different guidelines for the management of teratomas with raised AFP.

### In a child with a fully surgically resected, AFP-positive stage I malignant GCT, does an increase in serum AFP levels in follow-up confirm relapsed disease?

In the UK, for completely resected stage I malignant GCTs, an expectant 'watch-and-wait' policy

**Table 1** Summary of serum AFP and HCG levels frequently observed in different GCT subtypes

| GCT histological subtype | AFP | HCG |
|---|---|---|
| Yolk sac tumour | ++ | – |
| Germinoma | – | ± |
| Embryonal carcinoma | ± | ± |
| Choriocarcinoma | – | ++ |
| Teratoma | ± | – |

++, strongly positive levels; ±, levels may be negative or moderately positive; –, negative levels.
AFP, α-fetoprotein; GCT, germ cell tumour; HCG, human choriogonadotropin.

is employed with close clinical follow-up and serial AFP estimations, regardless of the initial AFP value. For AFP-positive cases, surveillance should be performed weekly until marker normalisation and then every 1–3 months until patients are 3 years off treatment. These sequential serum AFP estimations should be plotted on a logarithmic graph to ensure they fall at the expected rate following treatment (surgery, chemotherapy or both). Markers that increase or do not fall at the expected rate indicate resistant or relapsed disease (see figure 1) and warrant a change in management. As AFP is highly sensitive in such situations, with elevated levels often occurring before clinical or radiological evidence of GCT recurrence/relapse,[13] appropriate management changes should be instigated even in the presence of normal examination and imaging findings. Stage I malignant GCT cases that relapse are chemotherapy-naive and thus have an excellent outcome with treatment. However, the prognosis for relapsed GCT or hepatoblastoma disease pretreated with chemotherapy is more guarded.

### In a child with a GCT, hepatoblastoma or HCC, does the level of AFP at diagnosis, or rate of subsequent fall, affect outcome?

For GCTs, a retrospective study of extracranial childhood tumours identified serum AFP levels of ≥10 000 ng/ml at diagnosis as being associated with a worse prognosis, with 46% event-free survival (EFS) and 74% overall survival compared with 85% and 91%, respectively, for AFP <10 000 ng/ml.[14] As a result, the current Children's Cancer and Leukaemia Group guidelines for the UK management of extracranial GCTs utilise this diagnostic AFP cut-off, in combination with stage and histology, to assign risk groups and determine the use of either four or six chemotherapy courses. Whereas reports describing the AFP half-life in GCTs affecting adult patients are conflicting when considering clinical outcome, in paediatric practice those patients with a normal AFP decrease had an EFS of 89% compared with 63% for those who did not.[15]

For children with unresectable or metastatic hepatoblastoma, early changes in AFP levels have been shown to be a reliable predictor of outcome and may be used to identify poor treatment responders who should be considered for alternative therapies.[16] A report from the International Paediatric Oncology Society SIOPEL studies for hepatoblastoma demonstrated that a diagnostic serum AFP level of <100 ng/ml (<84 kU/l) identified a high-risk subgroup of patients with extensive disease at diagnosis, poor response to chemotherapy and poor outcome.[17] Using the same cut-off, the US Children's Oncology Group reported similar findings, with low AFP also associated with an increased risk of subsequent death.[18]

Due to the rarity of HCC in children, there are very few reports describing prognostic outcomes in such patients, and those that do exist often include hepatoblastoma and HCC cases together. Notwithstanding, very low or very high diagnostic AFP levels in childhood hepatoblastoma and HCC cases identified a worse outcome[19] and a small study of 12 unresectable paediatric hepatoblastoma and HCC cases requiring liver transplantation revealed that incomplete AFP response to chemotherapy appeared to be associated with decreased survival, although the numbers involved were very small.[20] Studies examining the clinical significance of the rate of AFP decline have not been performed in HCC to date.[21]

### In a child with Beckwith–Wiedemann syndrome (BWS), is screening for malignancy (in particular hepatoblastoma) with serum AFP justified?

Screening may be justified in certain conditions such as BWS, where the risk of developing a tumour in the first decade of life is 8.8%, with Wilms' tumour and hepatoblastoma the most common types.[22] Furthermore, isolated hemihyperplasia (IHH) also carries a risk of malignancy of 5.9% over the same timeframe.[22] In BWS and IHH, 3-monthly serum AFP estimation up until the age of 4 years is routinely carried out by some institutions to screen for hepatoblastoma.[22] However, it should be noted that in the postnatal period, AFP levels in BWS are generally higher, and decline at a slower rate, compared with healthy controls.[23] Some clinicians advocate 3-monthly abdominal ultrasound until 8 years of age in such cases to screen for hepatoblastoma and Wilms' tumour.[22] A report describing the detection of five cases of low-stage hepatoblastoma using this combined approach highlights the value of such a screening programme.[24] Furthermore, pancreatoblastoma, another rare embryonal tumour associated with BWS, also exhibits raised AFP levels at diagnosis,[25] reflecting its embryological origin from the gastrointestinal tract,[1] and may therefore be detected by such a screening approach. The decision to screen or not in such cases should be taken after discussion with the family and after considering the regular hospital visits, ultrasounds and blood tests involved.

### In a child with chronic liver disease, do elevated serum AFP levels suggest malignant transformation to HCC?

Raised serum AFP levels (>10 ng/ml) occur in ~75% of HCC cases.[26] However, the specificity of AFP is relatively low because moderately raised levels

**Table 2** Summary of alterations observed in maternal serum levels of multiple markers in the second trimester antenatal screening test for various fetal conditions

| | Condition | | |
|---|---|---|---|
| **Serum test marker** | **Down's syndrome (trisomy 21)** | **Edward's syndrome (trisomy 18)** | **Neural tube defect** |
| AFP | Low | Low | High |
| HCG | High | Low | NA |
| Unconjugated oestriol | Low | Low | NA |
| Dimeric inhibin-A | High | Low | NA |

AFP, α-fetoprotein; HCG, human choriogonadotropin.

may also be found in uncomplicated chronic liver disease.[26] Nonetheless, surveillance with serial AFP measurements and hepatic ultrasound have often been undertaken in patients with chronic liver disease with the intention of detecting malignant transformation, despite a lack of evidence that surveillance improves patient outcomes.[27]

### Antenatal screening

#### In pregnant women, does estimation of serum AFP reliably detect fetal anomalies?

In the early 1970s raised levels of AFP in cases of open neural tube defects were demonstrated in amniotic fluid and maternal serum, leading to a UK-wide study that confirmed the efficacy of serum screening for these defects between 10 and 24 weeks gestation.[28] However, the rapid development of real-time ultrasound technology has superseded AFP as the main screening modality for all fetal open neural tube defects. Furthermore, use of folate supplements during pregnancy has significantly reduced the incidence of such abnormalities. Conversely, it was observed that in conditions such as Down's syndrome, low levels of maternal serum AFP were often present, resulting in the development of biochemical screening for this condition. This involved the additional measurement of unconjugated oestriol and HCG in addition to AFP and was termed the 'triple test',[29] with subsequent demonstration of its efficacy in the early 1990s.[30] Use of all three markers in maternal serum early in the second trimester, along with maternal age, allowed calculation of the individual risk of a pregnancy carrying a fetus with chromosomal abnormalities, in particular Down's syndrome. A definitive diagnostic intervention, for example, amniocentesis, was offered where the risk was above a predefined cut-off, usually 1:250. In 1996, maternal serum dimeric inhibin-A (DIA) levels were shown to be altered in fetal chromosomal abnormalities and were suggested to increase their detection rate. Combined with AFP, HCG and unconjugated oestriol, this was termed the 'quadruple test'. However, this has not been widely adopted in the UK due to concerns about variability in DIA results, although an automated DIA assay has subsequently been developed. Table 2 summarises maternal serum levels of multiple markers in various fetal conditions. Recently, the National Health Service Fetal Anomaly Screening Programme introduced national standards that dictated that screening programmes must have a ≥75% detection rate with a false positive rate of <3% (http://fetalanomaly.screening.nhs.uk/). First trimester screening for maternal serum levels of pregnancy-associated plasma protein-A (PAPP-A) and HCG, combined with nuchal translucency ultrasound, has now superseded the triple test in many areas across the UK as it exceeds the national standard requirements. However, the second trimester triple test still retains an important screening role for those women who book too late for first trimester screening.[31]

## LIMITATIONS (WHAT ARE THE DRAWBACKS TO USING AFP?)

In antenatal screening, AFP values depend on accurate estimation of the gestational age of the fetus, in addition to whether the pregnancy is singleton or multiple. In the interpretation of AFP for potential cancer diagnosis, it should be remembered that AFP is not particularly specific, although it is sensitive for hepatoblastoma, HCC and subtypes of GCT. As described earlier, serum levels are raised physiologically in early infancy and may also be elevated in uncomplicated chronic liver disease,[26] following gastrointestinal tract/hepatic surgery or in certain conditions such as hereditary ataxia telangiectasia.[25] Isolated reports have also been described in infantile haemangioendothelioma[32] and may occur in rare gastrointestinal malignancies which have the potential for AFP production to be de-repressed. Interestingly, patients with GCTs have been reported to have false elevations of AFP, secondary to liver damage caused by chemotherapy, anaesthetic agents or other drugs.[33] Levels should therefore only be interpreted in light of a full history and examination, taking into account patient age, nature of presenting symptoms, past medical history, drug history including any potential recreational drug use and family history. Where possible hepatic disease is a clinical concern, AFP estimation should be performed with a full serum liver profile. Relevant radiological imaging will also assist in determining the likely cause of a pathologically elevated AFP level.

## POTENTIAL FUTURE RESEARCH (ARE THERE ALTERNATIVE WAYS TO IMPROVE AFP DETECTION? ARE THERE BETTER MARKERS THAN AFP?)

Although only a single gene codes for AFP, post-translational modifications including differential glycosylation generate several different isoforms (AFP-L1, AFP-L2 and AFP-L3) which are associated with the different tissues of origin (liver, gastrointestinal tract and yolk sac). In a paediatric study, despite raised total AFP in all cases, the AFP-L3 isoform distinguished hepatoblastoma and YST (high levels) from benign teratoma (low levels) in infancy.[34] AFP-L3 has also been shown to distinguish HCC from other chronic liver disease and in HCC is associated with a poor prognosis. However, lack of an automated detection method and the high costs of the reagents involved mean that it is not cost-effective and as a result, isoform testing has never become routine in the UK. The only centre in the UK currently offering this service for routine clinical use is based in Sheffield (http://www.immqas.org.uk/).

AFP (and/or HCG) are not universal markers of GCTs (see table 1). Recently, however, there has been much interest in microRNAs as potential

cancer biomarkers. These are short, non-protein coding RNAs that regulate gene expression by binding messenger RNA targets and which are dysregulated in cancer. The miR-371~373 and miR-302 clusters are universally over-expressed in all malignant GCTs, regardless of patient age, histological subtype or anatomical site,[35] and are not coordinately upregulated in other tumour types or disease states, demonstrating their sensitivity and specificity. Furthermore, serum levels of these microRNA clusters were elevated at malignant GCT diagnosis compared with normal serum.[36] Levels of miR-372 returned to normal during uneventful clinical follow-up, with similar kinetics to AFP.[36] In HCC, serum levels of miR-21, miR-122 and miR-223 were shown to be elevated compared with healthy controls, but were not specific, also being elevated in chronic hepatitis.[37] More work is therefore required in hepatoblastoma and HCC to identify microRNAs specific for those tumours rather than as a marker of non-specific liver injury.

## CLINICAL BOTTOM LINE

- α-Fetoprotein (AFP) levels should only be interpreted in the context of a full patient history and examination, considering patient age, presenting symptoms, past medical history, drug history and family history.
- Clinicians need to be aware of other conditions that may result in a raised AFP, including physiological elevations in the first 2 years of life.
- Second trimester maternal serum AFP estimation is being replaced by newer first trimester screening investigations with a higher detection rate and lower false positive rate.
- Serum AFP should be measured in the diagnostic work-up of any suspected germ cell tumour (GCT), hepatoblastoma or hepatocellular carcinoma (HCC). Serum human choriogonadotropin (HCG) should also be measured in possible GCTs.
- For suspected intracranial GCTs, serum and cerebrospinal fluid measurement of AFP and HCG should be performed prior to neurosurgical biopsy, as typical radiological imaging and positive markers may be diagnostic and obviate the need for invasive surgery.
- Serial AFP measurements may be used to assess response to cancer treatment and may be used for prognostication in GCTs, hepatoblastoma and HCC.
- Screening with 3-monthly serum AFP levels (and ultrasound imaging) for hepatoblastoma may be warranted in certain conditions such as Beckwith–Wiedemann syndrome and isolated hemihyperplasia.
- Three years of clinical and AFP marker follow-up should be undertaken for most malignancies associated with an increased AFP, plus imaging where appropriate.
- Due to limitations with specificity, AFP may be replaced by alternative markers in the future, such as serum microRNA quantification.

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